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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/823,864	04/13/2004	Terry B. Strom	1440.1024-002	5649

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
06/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,864	STROM ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 15-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 03/12/2007, has been entered.
Claim 13 has been amended.

Applicant's election of Group II and the species E anti-CTLA-4 antibodies in the Reply To Restriction Requirement, filed 03/12/2007, drawn to compositions comprising at least one costimulation blockade agent and rapamycin, is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

In view of applicant's amended claim 12 and applicant's Remarks, filed 03/12/2007, claim 12 drawn to compositions further comprising fish oil has been rejoined with Group II.

Claims 11-14 are under consideration as they read on the elected invention and species, drawn to the combination of rapamycin and anti-CTLA-4 antibodies.

Claims 1-10 and 15-21 have been withdrawn as being drawn to the non-elected invention and species.

2. No Information Disclosure Statement has been filed in the instant application.

3. Applicant should amend page 1 of the instant specification to update the status of the priority applications.
USSN 05/576,944 is now abandoned.

The instant claims appear to have an effective date of USSN 09/075,311, filed 05/08/1998.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Appropriate corrections are required

5. Claims 11-13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11-13 are indefinite in that the antecedent basis for "or a biological active derivative thereof" or "derivatives thereof" is ill-defined and confusing

For example, it is not clear whether "or a biological active derivative thereof" modifies the "agent" or "rapamycin" or both.

In turn, given the recitation of derivatives thereof in both claim 11 and 13, the antecedent basis of "derivatives thereof" in claim 13 is confusing as well.

Applicant should amend the claims to provide clarity to the claimed recitation of "derivatives".

Applicant should note the rejection set forth herein with respect to the 112, first paragraph, issues associated with derivatives.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

The antigen binding properties of a given antibody are principally encoded within the primary and tertiary structure of hypervariable or complementarity determining regions (CDRs). As well as varying in sequences, the lengths and conformations of these loops differ from one antibody to the next. It is known that for each antibody; the antigen binding properties are etched into the tertiary architecture of the combining site, antibody structure itself guides the selection by via affinity in the screening assays, not based upon the primary amino acid sequence alone. There is high sterochemical complementarity between the surfaces of the bound antigen and the antibody combining site.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences, including alterations in the amino acids of antibodies can abolish antigen binding or specificity. For example, a single amino change in an immunoglobulin can have profound effects on the antigen bind specificity and properties of an antibody.

Given that the specification discloses that amino acid alterations are encompassed by the claimed recitation of "derivatives" (e.g., see page 14, paragraph 3 of the specification), applicant has not provided sufficient guidance and direction to those amino acid variations in anti-CTLA-4 antibodies that would permit retention of antigen-binding.

Further, given the high polymorphism of antibodies, applicant has not provided sufficient guidance and direction to those amino acid variations among the scope of anti-CTLA-4 antibodies, broadly encompassed by the claimed invention.

Also, it was unlikely or unpredictable that functional antibodies and their fragments as they read on "derivatives" would be expected to maintain the required binding specificity and functions associated with anti-CTLA-4 antibodies with any amino acid modifications, in the absence of sufficient guidance and direction in the specification as filed.

Applicant has provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing ant-CTLA-4 antibodies which can retain their binding to CTLA-4 based upon the insufficient guidance and direction as to those amino acids permitted to maintain CTLA-4-specific binding by the scope of derivatives of anti-CTLA-4 antibodies broadly encompassed by the claimed invention. Such antibodies would not necessarily have the required conformation for antigen-binding function. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody "derivatives" as broadly as is claimed.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to the use of the claimed anti-CTLA-4 antibody "derivatives which require their ability to retain their binding to CTLA-4 in therapeutic utilities in the absence of sufficient guidance and direction in the specification as filed. Undue experimentation would indeed be required to produce the invention commensurate with the scope of the claimed invention.

Applicant is invited to simply recite anti-CTLA-4 antibodies and the appropriate functional fragments, provided there is sufficient written description in the specification as file.

Further, it is noted that the "rapamycin derivatives" appear to be enabled, given the disclosure on pages 10-11, overlapping paragraph of the instant specification.

As indicated above in the rejection under 35 USC 112, second paragraph, and here in the rejection under 35 USC 112, first paragraph,
applicant is invited to amend the claims to clearly address these issues and the distinction between "rapamycin derivatives" and "antibody derivatives".

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 11 and 13-14 are rejected under 35 U.S.C. § 102(e) as being anticipated by Cottens et al. (U.S. Patent No. 5,985,890) (see entire document).

Cottens et al. teach pharmaceutical compositions, including kits/packages for use in inflammation or immunosuppression in subjects in need thereof comprising rapamycin and rapamycin derivatives and immunosuppressive antibodies (e.g., see column 18), including anti-CTLA4 antibodies (e.g. see columns 17-18, overlapping paragraph). See Columns 1-13 for a more discussion concerning rapamycin and its derivatives as potent therapeutic having immunosuppressive, anti-tumor and anti-fungal properties (e.g., see columns 1 and 13-19 in particular).

11. Claims 11 and 13-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable Cottens et al. (U.S. Patent No. 5,985,890) in view of Kelley et al. (U.S. Patent No. 5,118,493).

Cottens et al. teach pharmaceutical compositions, including kits/packages for use in inflammation or immunosuppression in subjects in need thereof comprising rapamycin and rapamycin derivatives and immunosuppressive antibodies (e.g., see column 18), including anti-CTLA4 antibodies (e.g. see columns 17-18, overlapping paragraph). See Columns 1-13 for a more discussion concerning rapamycin and its derivatives as potent therapeutic having immunosuppressive, anti-tumor and anti-fungal properties (e.g., see columns 1 and 13-19 in particular) (see entire document).
Cottens et al. differs from the claimed compositions and kits by not disclosing fish oils in such pharmaceutical compositions and kits.

Kelley et al. teach the use of vehicles comprising fatty acids component of the omega-3, wherein the source is fish oil, in reducing nephrotoxicity of said compounds (see entire document, including Background of the Invention and Description of the Preferred Embodiments, including column 9).

Given the decreased nephrotoxicity and concomitant improvement in therapy associated with fish oils in immunosuppressives such as cyclosporine as taught by Kelley et al. (e.g., see column 9, paragraph 8 and Examples and Discussion), one of ordinary skill in the art at the time the invention was made would have been motivated to select fish oil to provide similar beneficial effects to an immunosuppressive agent such as rapamycin, also known to have unwanted side effects in immunosuppressive regimens at the time the invention was made. The ordinary artisan would have had an expectation of success in providing compositions comprising fish oil to immunosuppressive drugs such as rapamycin, given the use of multiple pharmaceutical compositions comprising rapamycin and the use of said fish oil in pharmaceutical compositions at the time the invention was made.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at *12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to provide compositions and kits comprising rapamycin and anti-CTLA-4 antibodies for immunosuppressive regimens, combining said immunosuppressives, particularly rapamycin, with fish oil to increase bioavailbility and to decrease deleterious side-effects of said immunosuppressives was routine to the ordinary artisan at the time the invention was made and therefore obvious in designing such pharmaceutical compositions and kits comprising immunosuppressive agents.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary

12. No claim allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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